REMARKS

Amendment to the Specification

The title has been amended to read "Combination Therapy Comprising ZD6474 and Gemcitabine for Anti-Cancer Therapy" as suggested by the Examiner at page 3 of the Action.

Claim Amendments

The claims have been amended above in a manner that is believed to place all claims in condition for allowance. Specifically:

Claims 2 and 10 have been amended to be specifically directed toward a method for the treatment of pancreatic cancer, in that the Examiner has found that the specification is enabling for the reduction of tumor growth in pancreatic cancer at pages 5-6 of the specification.

Claims 1, 3, 9 and 11, directed more broadly toward a method for the production of an antiangiogenic and/or vascular permeability reducing effect or a method for the treatment of a cancer involving a solid tumour, have been cancelled, without prejudice, in order to expedite the prosecution of this application toward allowance.

Claims 6-8 and 12-14 have been cancelled in that they were in a "use" format not generally accepted under U.S. practice.

These amendments are made without waiver or prejudice to Applicant's right to prosecute any deleted subject matter in one or more continuing applications. It should be clear from the above that no new matter has been added and entry of these amendments is therefore believed to be appropriate and is respectfully requested.

Following entry of the above amendments, claims 2, 4, 5 and 10 remain pending in this application.

Specification Objections

The title of the invention has been objected to as not being "descriptive," and the Examiner has suggested an alternative title. Applicant has adopted the Examiner's suggested

Title which has been implemented by the above amendment to the Title. This ground for objection therefore has been overcome.

Claim Rejections - 35 USC § 101

Claims 6-8 and 12-14 have been rejected as being in a "use" format not generally accepted under U.S. practice. This rejection has been obviated by the cancellation of these claims.

Claim Rejections - 35 USC § 112, 1st Paragraph

Claims 1 and 9 have been rejected under 35 USC § 112, 1st paragraph, as failing to comply with the enablement requirements. Specifically, the Examiner asserts that Applicant "has not shown how the method of the instant case would affect antiangiogenic or vascular permeability effects in any way, and thus one of skill in the art would not be able to use the composition of the instant case to use the invention as claimed." Although Applicant disagrees with the Examiner's conclusion, claims 1 and 9 have been cancelled in order to expedite prosecution of this application to allowance.

The Examiner has also rejected claims 2-3 and 10-11, under 35 USC § 112, 1st paragraph, asserting at pages 5-6 of the Action that "the specification, while being enabling for the reduction of tumor growth in pancreatic cancer, does not reasonably provide enablement for treatment of cancer as a whole." Although Applicant disagrees with the Examiner on this point as well, claims 2 and 10 have been amended to be specifically directed toward the treatment of pancreatic cancer and claims 3 and 11 have been cancelled.

It is therefore respectfully submitted that these rejections under section 112, 1st paragraph have been overcome, and the withdrawal of this ground for rejection is respectfully requested.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The rejection of claims 1 and 9 and claims 6-8 and 12-14 as being indefinite has been obviated by the cancellation of these claims, without prejudice, for the reasons noted above.

Claim Rejections - 35 USC § 103

At pages 9-11 of the Action, claim 1, 2, 4-8 and 12-14 are rejected under 35 USC § 103(a) as being unpatentable over Bruns *et al.* (cited by Applicant on page 3 of the specification) in view of Sepp-Lorenzino *et al.* This ground for rejection has been obviated with respect to claims 1, 6-8 and 12-14 by the cancellation of those claims.

With respect to claim 2 (which has been narrowed to the treatment of pancreatic cancer by the above amendments) the Examiner argues that both Bruns *et al.* and Sepp-Lorenzino *et al.* teach drugs that are useful for treatment of various cancers, and that angiogenesis is known to play a role in cancer, and concludes that "for the reasons discussed above it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute ZD6474 for DC101 in the method of Bruns *et al.* due to the potency of ZD6474 and its known antiangiogenic properties."

With respect to claims 4 and 5, which claim a pharmaceutical composition and a kit comprising ZD6474 and gemcitabine, the Examiner argues that "since the method of treatment of cancer with that combination is obvious as discussed supra, the composition and the use of the composition in a "kit" form is obvious as well."

Applicant respectfully disagrees with the Examiner's conclusion, and submits that it would not be possible to predict the surprising results obtained by Applicant by combining ZD6474 and gemcitabine. Bruns *et al.* relates to a combination of DC101, an antibody directed to the extracellular domain of VEGF-R2. This is a very different agent to ZD6474 which is a tyrosine kinase inhibitor so it interacts with the intracellular domain and has inhibitory activity against both VEGF-R2 and the epidermal growth factor receptor (EGF-R). Therefore, the skilled person is going to derive little teaching from Bruns *et al* as to the efficacy of combining ZD6474 with gemcitabine. Sepp-Lorenzino *et al*, as pointed out by the Examiner, has some information about gemcitabine. It is submitted that this would not direct the skilled person to the presently claimed combinations and methods. The Examiner points to Page 1450 where the text refers to a combination with a different agent, SU5416, however, this agent has a different profile to ZD6474, being almost equipotent at inhibiting PDGF-Receptor-β. In any event the phase I trial was terminated so the skilled man would find little teaching with respect to ZD6474. The

Examiner also points to page 1455, column 2 where text refers to aa combination with CEP7055. Again this agent has a very different profile to ZD6474 inhibiting Flt-1 and Flt-4 with comparable potentices to KDR. Therefore, the skilled person would find little teaching with respect to ZD6474.

The teaching of Bruns *et al* combined with Seppo-Lorenzino *et al* also does not give any teaching to the skilled person as to the surprising results obtained by the combination of ZD6474 in combination with gemcitabine. To help illustrate this unexpected result, the Examiner's attention is drawn to the attached copy of Conrad *et al* (2007), which is a literature publicaiton of the data on which the present application was based.

The studies included in the present application and in Conrad *et al* show ZD6474, when combined with gemcitabine, produces a greater inhibition of tumour growth that either treatment alone. Gemcitabine and ZD6474 inhibit tumour growth to 68% and 44% of the controlled whereas the combination is significantly better inhibiting tumour growth to 25% of the control. The combination of gemcitabine and ZD6474 also has highly significant effects on the development of secondary tumours compared to either agent alone (see Table 1 in Conrad *et al* which corresponds to Table 1 of the present application). Of particular interest is a novel observation of the effect on lymph node metastasis (see page 578, column 1, lines 47-49 of Conrad *et al*) which is not seen with the antibody DC101. Therefore in light of the surprising results it is respectfully submitted that any case of *prima facie* obviousness of present claims that may be asserted over the combination of Bruns *et al* and Seppo-Lorenzino *et al.* has been overcome.

At pages 11-12 of the Action, claims 9 and 10 are rejected under 35 USC § 103(a) as being unpatentable over Bruns *et al.* in view of Sepp-Lorenzio *et al.* in further view of Ostruszka *et al.* This ground for rejection has been obviated with respect to claim 9 by the cancellation of that claim. Claim 10 has been narrowed by the above amendments to the treatment of pancreatic cancer.

The Examiner notes that claims 9 and 10 are the same as claims 1 and 2 respectively, except that claims 9 and 10 further add the composition is administered before, after or simultaneously with an effective amount of ionizing radiation. The Examiner acknowledges that neither Bruns *et al.* nor Sepp-Lorenzino *et al.* teach the combination therapy including use of

ionizing radiation, but asserts that "the use of ionizing radiation in cancer therapy is well known and it is often used in combination with anti-cancer drugs such as those in the instant invention."

The Examiner thus cites Ostruszka *et al.* as teaching that "gemcitabine (also referred to as dFdCyd) can be used in combination with ionizing radiation (abstract) and that gemcitabine is a potent radiosensitizer (abstract)," and concludes that "one of ordinary skill in the art at the time of the invention would be aware of ionizing radiation and the fact that it works in combination with anti-cancer drugs such as gemcitabine, and thus it would have been obvious to one of ordinary skill at the time of the invention [to] also add ionizing radiation to the combination therapy in claims 1 and 2 and thus claims 9 and 10 are unpatentable over Bruns et al. in view of Sepp-Lorenzino et al., in further view of Ostruszka et al." (Action at page 12).

Applicant again respectfully disagrees with this assertion in that the combined disclosures of Bruns *et al.*, Seppo-Lorenzino *et al.* and Ostruszka *et al.* do not teach or suggest to the skilled person the surprising results obtained by Applicant by the combination of ZD6474 with gemcitabine further comprising ionizing radiation. To illustrate this, a copy of Bianco *et al.* (2006) is attached, which relates to studies in pancreatic cancer for a combinations of ZD6474 and gemcitabine and combinations of ZD6474, gemcitabine and ionizing radiation. The Examiner's attention is particularly drawn to Figure 4 on page 7105 of Bianco *et al.* which shows the mean tumour volume during and after treatment with these combinations. It can be seen from this Figure that there is a significant improvement with a combination of ZD6474 and gemcitabine compared to either agent alone, and a very marked further improvement is realized by adding ionizing radiation to ZD6474 and Gemcitabine. Therefore in light of these unexpected results it is respectfully submitted any assertion of *prima facie* obviousness that might be advanced from the combination of Bruns *et al.*, Seppo-Lorenzino *et al.* and Ostruszka *et al.* has been overcome by the unexpected significant improvement achieved by the combinations as presently claimed.

At pages 12-13 of the Action, claims 3 and 11 are rejected under 35 USC § 103(a) as being unpatentable over Bruns *et al.* in view of Sepp-Lorenzio *et al.* in further view of Ostruszka *et al.* in further view of Burton *et al.* This ground for rejection has been obviated with respect to claims 3 and 11 by the cancellation of those claims. Nevertheless, in view of the amendments to

claims 2 and 10 directing them to the treatment of pancreatic cancer (a species of solid tumour, see, *e.g.*, specification at page 11, lines 5-7) this further ground for rejection will be addressed.

The Examiner notes that although neither Bruns *et al.* nor Sepp-Lorenzino *et al.* explicitly state whether their methods can be used on solid tumors, Ostruszka *et al.* teach that gemcitabine has clinical activity in treatment of solid tumors (pointing to page 6080, paragraph 1) and Burton *et al.* teach that ZD6474 can be used on solid tumors (pointing to page 12, table 13). From this four-reference combination the Examiner concludes that "it would have been obvious to one of ordinary skill in the art at the time of the invention that if the combination of ZD6474 and gemcitabine can be used to treat cancer as discussed supra, and both drugs are individually known to treat solid tumors, that the combination would be expected to also treat solid tumors." However, in view of the unexpected significantly improved results demonstrated by the comparative data discussed above, it would *not* have been obvious to one of ordinary skill in the art to combine ZD6474 and gemcitabine, and there is nothing in Burton *et al.* that would teach or suggest this unexpected result from the presently claimed combination discovered by Applicant.

Information Disclosure Statement

The Examiner has noted that the form PTO 1449 submitted with the filing of this application on April 7, 2005 failed to comply with the requirement of 37 CFR 1.98(a)(2). However, at the time this form PTO-1449 was submitted, the International Bureau generally forwarded copies of the documents cited in the International Search Report to the US Patent and Trademark Office at the time the International Application was ready for entry into the US National Stage. However, it appears the document copies were not forwarded by the International Bureau in the present application. Accordingly, the undersigned will submit an Information Disclosure Statement and form PTO-1449 citing and submitting a copy of each of the ISR cited documents as soon as copies of these literature references are available to the undersigned.

Conclusion

All grounds for rejection having been addressed and, it is believed overcome, by the above amendment, arguments an comparative evidence, it is submitted that all presently pending claims are in condition for allowance, and a notice to that effect is respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 4, 2008 By: _____

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001